Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations

Wolf, Nicole I ; Vanderver, Adeline ; van Spaendonk, Rosalina M L ; Schiffmann, Raphael ; Brais, Bernard ; Bugiani, Marianna ; Sistermans, Erik ; Catsman-Berrevoets, Coriene ; Kros, Johan M ; Pinto, Pedro Soares ; Pohl, Daniela ; Tirupathi, Sandya ; Strømme, Petter ; de Grauw, Ton ; Fribourg, Sébastien ; Demos, Michelle ; Pizzino, Amy ; Naidu, Sakkubai ; Guerrero, Kether ; van der Knaap, Marjo S ; Bernard, Geneviève

Abstract: OBJECTIVE: To study the clinical and radiologic spectrum and genotype-phenotype correlation of 4H (hypomyelination, hypodontia, hypogonadotropic hypogonadism) leukodystrophy caused by mutations in POLR3A or POLR3B. METHODS: We performed a multinational cross-sectional observational study of the clinical, radiologic, and molecular characteristics of 105 mutation-proven cases. RESULTS: The majority of patients presented before 6 years with gross motor delay or regression. Ten percent had an onset beyond 10 years. The disease course was milder in patients with POLR3B than in patients with POLR3A mutations. Other than the typical neurologic, dental, and endocrine features, myopia was seen in almost all and short stature in 50%. Dental and hormonal findings were not invariably present. Mutations in POLR3A and POLR3B were distributed throughout the genes. Except for French Canadian patients, patients from European backgrounds were more likely to have POLR3B mutations than other populations. Most patients carried the common c.1568T>A POLR3B mutation on one allele, homozygosity for which causes a mild phenotype. Systematic MRI review revealed that the combination of hypomyelination with relative T2 hypointensity of the ventrolateral thalamus, optic radiation, globus pallidus, and dentate nucleus, cerebellar atrophy, and thinning of the corpus callosum suggests the diagnosis. CONCLUSIONS: 4H is a well-recognizable clinical entity if all features are present. Mutations in POLR3A are associated with a more severe clinical course. MRI characteristics are helpful in addressing the diagnosis, especially if patients lack the cardinal non-neurologic features.

DOI: https://doi.org/10.1212/WNL.0000000000001002

DOI: https://doi.org/10.1212/WNL.0000000000001002